

REMARKS

Claims 1-6, 8-12, 14, 15 and 17-22 currently appear in this application. Claims 1-6, 8, 9, 11, 12, 14, 15, 17 and 18 have been withdrawn. The Office Action of April 29, 2008, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Claims 7, 10, 13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jackson et al., US 5,807,586 in view of Schlipalius, IS 6,132,790.

This rejection is respectfully traversed. Claims 7, 10, 13 and 16 have been replaced by new claims 19-22. Claims 19-22 recite a method for reducing the undesirable effects of hormone replacement therapy while simultaneously providing positive effects of hormone replacement therapy, by administering a composition comprising at least one phytoestrogen and a mixture of a mixture of lycopene, phytofluene and/or phytoene.

Jackson, on the other hand, teaches a complex mixture of active substances for use in dietary supplementation of women at various life stages (pre-menopausal, menopausal, and post-menopausal). As such,

Jackson teaches the simultaneous administration of many different active ingredients which, as explained in Jackson, have a beneficial effect of preventing or reducing life-stage associated health risks (column 2, lines 30-31), including the risk of some cancers. The active ingredients which are described as having cancer-preventing or cancer-reducing effects include:

Folic acid (column 5, lines 21-26)

Vitamin C (column 5, lines 54-57) and

Phytoestrogens (column 6, lines 33-39).

Other active substances which form compulsory constituents of the preferred compositions disclosed in Jackson include calcium, magnesium, boron, copper, manganese, zinc, vitamin D, iron, vitamin B12, vitamin B6, chromium and vitamin E.

The present claims clearly restrict the administered composition to a composition substantially containing no active ingredients other than the phytoestrogen(s) and carotenoid(s). This is clearly recited in each of claims 19-22.

There is no way that one skilled in the art reading Jackson would be motivated to limit the composition solely to phytoestrogens and carotenoids. The method claimed herein is

to reduce the undesirable effects of hormone replacement therapy while simultaneously providing positive effects of hormone replacement therapy, while Jackson discloses a method for dietary supplementation during different life stages of a woman.

There herein claimed method is clearly concerned with a single, clearly defined aim: the reduction of the undesirable effects inherent in hormone replacement therapy, this reduction being the result of administration of a single active anti-cancer agent, namely, a carotenoid or mixture of carotenoids. It is respectfully submitted that Jackson does not unequivocally teach the use of one or more carotenoids for this purpose, and furthermore, provides no enabling disclosure for such a use. It is therefore by no means obvious from a reading of Jackson that administering one or more carotenoids as the sole active ingredients would have the desired effects, that it, reduction of HRT-related side effects.

Another difference between Jackson and the presently claimed method is found in relation to the identity of the administered carotenoid(s) as well as the doses thereof. Thus, while Jackson does provide for optional use of one or more carotenoids, these are generally and preferably carotenoids having substantial vitamin A activity, "provitamin A."

Optionally, the dietary supplements of this invention may further contain an amount of vitamin A or mixed carotenoids sufficient to supplement the nutritional needs of a woman at a particular life stage. Vitamin A may be provided as pre-formed vitamin A or as mixed carotenoids, or both. There are more than 500 naturally occurring carotenoids, about 50 of which can serve as precursors of retinol and therefore have provitamin A activity [column 6, line 53 to column 7, line 3].

As described in paragraph 39 of the present application, the scope of the method claimed herein is clearly limited to co-administration of phytoestrogens with one or more carotenoids of the type which do **not** have substantial vitamin A activity: "Where the composition of the present invention comprises at least one phytoestrogen, the carotenoid is preferably one which does not exhibit substantial provitamin A activity. Carotenoids which do not exhibit substantially provitamin A activity include, for example lycopene, zeta-carotene, phytoene, phytofluene, lutein, and zeaxanthin."

It is clear that the carotenoids administered in the presently claimed methods are non-provitamin A carotenoids, unlike those disclosed in Jackson.

Although Jackson discloses the possibility of using non provitamin A carotenoids, such as lycopene and lutein, no details concerning the required doses of these carotenoids or the serum levels achieved are provided. Furthermore, both of

the journal references provided in support of the known effects of lycopene on cervical cancer (column 7, lines 8 and 9) relate to the correlation of cervical cancer risk with serum concentrations of lycopene and lutein following normal dietary intake of these carotenoids. Thus, these publications, even if incorporated by reference in the disclosure of Jackson, do not provide any teaching regarding the amount of non-vitamin A carotenoid to be optionally incorporated into the dietary mix of Jackson.

Schlupalius adds nothing to Jackson, because Schlupalius only discloses methods for making a safe source of vitamin A by making a carotenoid composition containing a carotenoid in an oil solvent, a dispersion of a water dispersible matrix and a stabilizer, and an emulsifier. This has absolutely nothing to do with ameliorating the effects of HRT.

The herein claimed method, however, relates to administering a carefully demined amount of carotenoid in an amount to produce a particularly claimed serum concentration following such administration. The need for accurate control of the amount of administered carotenoid is illustrated in Figure 5 of the instant application, from which it may be seen that high concentrations of lycopene (such as 5 micromolar) result in a very high level of inhibition of phytoestrogen-

induced cell proliferation. This level of inhibition is so great that it results in a cell proliferation rate that is lower than the non-stimulated control. Since the herein claimed method is to inhibit only the undesirable effects of HRT, it is important that the serum levels of lycopene and/or the other carotenoids used are such that they cause reduction of phytoestrogen-stimulated cell proliferation to a significant degree, thereby preventing the development of cancerous conditions associated with HRT, without reducing the proliferation rate of sub-normal levels. Serum concentrations of up to 1.5 micromolar (corresponding to a daily administration of about 2 mg of carotenoid(s)) was selected, on the basis of experimental results obtained by the inventors, as optimal for the requirements of the presently claimed method. It is respectfully submitted that this important aspect of the claimed method is neither taught nor suggested by Jackson or Schlipalius, either alone or in combination.

It should also be noted that the carotenoid mixture administered by the presently claimed method has a synergistic effect. An example of this synergistic effect is shown in Figure 6 of the present application, in which the unexpectedly greater-than-additive effect of a combination of lycopene and phytoene on cell proliferation is shown. In view of the fact

that Jackson is completely silent regarding such a synergistic effect, and indeed does not even teach defined combinations of specific carotenoids, it is respectfully submitted that this combination cannot reasonably be considered to be obvious in view of the cited patents.

There is nothing in Schlupalius that either explicitly teaches or even hints at the specific combinations of lycopene, phytoene and/or phytofluene as claimed herein. Rather, Schlupalius teaches at column 3, lines 10-19, an emulsion containing carotenoids selected from the group consisting of fat soluble retinoids, beta-carotene, lutein, lycopene, astaxanthin, canthaxanthin, phytoene, alpha-carotene, ap-carotenal, retinol, capstanthin, oleo resin paprika, zeaxanthin, beta-cryptoxanthin, phytofluene, gamma-carotene and natural carotenoid isolates and mixtures thereof. In fact, Schlupalius is only concerned with the technical steps involved in producing a carotenoid-containing emulsion, and provides no teaching whatsoever for the specific synergistic effect of the specific carotenoid compositions claimed herein. Thus, Schlupalius adds nothing to Jackson.

Claims 7, 10, 13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlupalius in view of Gorbach, US 5,498,631 or Gaynor et al., US 5,904,924.

This rejection is respectfully traversed.

Schlupalius merely discloses a composition of carotenoids, but is completely silent with respect to how these compositions are used. It is respectfully submitted that method claims cannot be rendered obvious by composition claims wherein there is no guidance of how the composition is to be used.

Gorbach adds nothing to Schlupalius, as Gorbach provides absolutely no teaching, hint, or suggestion regarding the beneficial effects of carotenoids in managing PMS, Menopause, or, particularly HRT-related side effects. Rather, Gorbach teaches a method for treating the symptoms of menopause and PMS by administering an isoflavonoid including the phytoestrogens disclosed and taught in the present method. However, it is noted that whereas Gorbach teaches administering phytoestrogens in order to treat these conditions, the herein claimed method administers carotenoids to prevent or reduce the undesirable effects caused by simultaneous administration of phytoestrogens. Thus, if one combines the teaching of Schlupalius and Gorbach, as suggested by the Examiner, one skilled in the art would arrive at a method of treatment in which both phytoestrogens (Gorbach) and carotenoids (Schlupalius) act "in the same direction." That is, both of said substances would act to prevent or inhibit the undesirable effects caused by other agents present in the



body of the patient being treated. This is the complete opposite of the method claimed herein, in which phytoestrogens are administered as HRT agents and **which are expected to actually cause the undesirable side effects** It is the carotenoids of the presently claimed method that provide the sole means for preventing or reducing these side effects.

Gaynor, which teaches compositions comparing *inter alia* phytoestrogens, also mentions that phytoestrogens may act to inhibit or reduce the development of cancerous conditions (column 3, lines 2-5). However, as explained in the present application at paragraphs 0005 and 0006, phytoestrogens exert their anti-proliferative effects when used at high doses that result in high, super-physiological blood concentrations. This contrasts with the physiologically effective amounts of phytoestrogen administered in the herein claimed methods. At the much lower concentrations as claimed herein, the phytoestrogens have been found to increase the risk for development of hormone-dependent cancers, as described at paragraph 007 of the present specification.

Consequently, administering a combination of the phytoestrogens taught in Gaynor with the carotenoids of Schlipalius would not be suitable for use in the HRT method as claimed herein, at least for the reason that the proliferation-preventing dose of phytoestrogen would be too

high to provide the desired physiologically relevant hormone replacement effect. Moreover, as Schlipalius only discloses carotenoid compositions, and not methods of using these compositions, one skilled in the art would find no motivation to combine the Schlipalius compositions with those of Gaynor.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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